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**Overweight young female kidney donors have low renal functional reserve post-donation**

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## Abstract

Maintenance of adequate renal function after living kidney donation is important for donor outcome. Overweight donors in particular may have an increased risk for end stage kidney disease (ESKD), and young female donors have an increased preeclampsia risk. Both of these risks may associate with low post-donation renal functional reserve (RFR). Because we previously found that higher BMI and lower post-donation RFR were associated, we now studied the relationship between BMI and RFR in young female donors. RFR, the rise in GFR ( $^{125}\text{I}$ -Iothalamate clearance) during dopamine, was measured in female donors (<45 years) before and after kidney donation. Donors who are overweight (BMI>25) and non-overweight donors were compared by t-test; the association was subsequently explored with regression analysis. We included 105 female donors (age 41 [36-44] (median[IQR])) with a BMI of 25 [22-27] kg/m<sup>2</sup>. Pre-donation GFR was 118 (17) ml/min (mean(SD)) rising to 128 (19) ml/min during dopamine; mean RFR was 10 (10) ml/min. Post-donation GFR was 76 (13) ml/min, rising to 80 (12); RFR was 4 (6) ml/min ( $p<0.001$  vs. pre-donation). In overweight donors, RFR was fully lost after donation (1 ml/min vs. 10 ml/min pre-donation,  $p<0.001$ ), and BMI was inversely associated with RFR after donation, independent of confounders (St.  $\beta$  0.37,  $p=0.02$ ). Reduced RFR might associate with the risk of preeclampsia and ESKD in kidney donors. Prospective studies should explore whether RFR is related to preeclampsia and whether BMI reduction prior to conception is of benefit to overweight female kidney donors during and after pregnancy.

## Introduction

Living donor kidney transplantation is the preferred treatment for patients with end-stage kidney disease (ESKD), providing better outcomes compared to either dialysis or transplantation of a kidney from a deceased donor(25). Although efficient living donor programs have been established, a shortage of donor organs still exists, which has led to liberalization of selection criteria for the living donor(29). Nowadays, donors with a high body mass index (BMI) are more often eligible for donation, leading to an increased number of obese donors(24). However, donors may have an increased risk for ESKD, in particular when they are obese(23).

After kidney donation, vasodilation occurs in the remaining kidney as a compensatory response to maintain glomerular filtration rate (GFR) (21); as a logical consequence, the vasodilatory reserve capacity decreases(31, 39, 41). In 2008, Rook et al. showed that in living kidney donors, a higher donor BMI was associated with loss of renal functional reserve (RFR). This was assessed as the dopamine response, also known as reserve capacity(32). RFR was fully lost in older donors with BMI > 30 kg/m<sup>2</sup>, while they maintained an adequate GFR in the short term. However, the implication of loss of RFR for long-term outcomes in obese donors has not yet been established.

Obesity is also a major risk factor for preeclampsia (PE). Of note, Garg et al. reported a significantly increased risk to develop gestational hypertension or preeclampsia (PE) (15), extending earlier survey data (18, 30). During normal pregnancy renal blood flow and GFR increase during the first half of pregnancy (8, 19, 22). Absence of pregnancy-induced renal vasodilation and absence of the hyperfiltration of pregnancy are hallmarks of PE (8, 12,28). A low RFR in young female donors, as a possible indicator of reduced renal vasodilator

69 capacity, may therefore be relevant to the findings by Garg et al. and others on PE risk (15,  
70 18, 30).

71 Due to the low number of young female kidney donors included in the 2008 study, Rook et  
72 al. mainly found an effect in older donors and were unable to draw conclusions on either loss  
73 or preservation of RFR in women of childbearing age (32). We hypothesized that renal RFR  
74 is lost in overweight young female donors after donation. In the current study, therefore, we  
75 studied the relationship between BMI and renal RFR by dopamine response before and after  
76 donation in female donors of childbearing age.

77

## Materials and Methods

We performed a retrospective cohort study, consisting of 105 living female kidney donors between 18 and 45 years old, who donated between 1992 and 2016 at the University Medical Center Groningen. Data was collected from the living donors screening and follow-up program in our center, at four months before and two months after donation. The study was approved by the institutional review board (METc 2014/077) and was conducted in accordance with the declaration of Helsinki.

### *Renal function measurements*

Kidney function was measured using  $^{125}\text{I}$ -Iothalamate and  $^{131}\text{I}$ -hippurate infusion as described (32): Measurements were performed in a quiet room, with the subject in semi-supine position. After drawing a blood sample,  $^{125}\text{I}$ -Iothalamate and  $^{131}\text{I}$ -hippurate infusions were given (0.04 mL/kg containing 0.04 MBq and 0.03 MBq respectively). At 08.00 hour 0.6 MBq of  $^{125}\text{I}$ -Iothalamate was administered, followed by continuous infusion of 12 mL/h. After a two-hour stabilization period, baseline measurements started in a steady state of plasma tracer levels. Clearances were calculated as  $(U \cdot V)/P$  and  $(I \cdot V)/P$ , where  $U \cdot V$  represents the urinary excretion,  $I \cdot V$  represents the infusion rate of the tracer and  $P$  represents the plasma tracer concentration per clearance period. From clearance levels of these tracers, GFR, effective renal plasma flow (ERPF) and filtration fraction (FF) were calculated. Correction for incomplete bladder emptying and dead space was achieved by multiplying the urinary  $^{125}\text{I}$ -Iothalamate clearances with plasma and urinary  $^{131}\text{I}$ -hippurate clearance. Day-to-day variability of GFR is 2.5% (1).

Renal functional reserve (RFR), expressed as the change in GFR in ml/min, was measured by extending the above-mentioned procedure by two hours with a dopamine infusion of 1.5  $\mu\text{g/kg/min}$  (38).

#### *Clinical and biochemical measurements*

At both time points, height, weight and blood pressure measurements were collected. Conforming to selection criteria of our kidney donor program, all donors were normotensive or had adequately regulated blood pressure with a maximum of one antihypertensive drug. Use of anti-hypertensives was very low (3%); adjustment of the analysis for use of anti-hypertensives did not change the conclusions, and is therefore not included in this paper. Furthermore, subjects with a history of diabetes (or an abnormal glucose tolerance test), kidney disease or cardiovascular events were excluded from kidney donation. Use of contraceptives (9%) was underreported and not included in our analysis. BMI was calculated as  $(\text{body weight}/\text{height}^2)$ , where a  $\text{BMI} \geq 25 \text{ kg/m}^2$  was considered as being overweight. Proteinuria ( $\text{g}/24\text{h}$ ) was measured from 24-hour urine collection by a standard assay.

#### *Statistical analysis*

Data are reported as mean (standard deviation, SD) for normally distributed variables and median [interquartile range, IQR] for skewed data. Binary variables are shown as “number (%)”. GFR data are reported as absolute values ( $\text{mL/min}$ ) and normalized for body surface area (BSA;  $\text{mL/min}/1.73\text{m}^2$ ) as well as height ( $\text{mL/min}/\text{m}$ ). This was done because BSA and BMI are strongly correlated. Accordingly, BSA-adjustment, although customary in the literature, induces a systematic error in analyses for possible associations with BMI(10). In line with prior papers(4) we therefore report height-normalized values along with BSA-normalized values. RFR is reported as change in GFR in  $\text{mL/min}$  during dopamine infusion.

122 A t-test was used to determine differences between normal and overweight kidney donors,  
123 after transformation of skewed data. If data remained skewed after transformation, a Mann-  
124 Whitney U test was performed. To investigate association between BMI and RFR after  
125 donation, linear regression analysis was performed with BMI as independent and difference  
126 in RFR as dependent variable. We adjusted for potential confounders (GFR, age) in  
127 subsequent multivariable analysis. Statistical analyses were performed by SPSS version 22  
128 for Windows (IBM, Armonk, NY) and Graphpad Prism 6 for Windows (Graphpad, San  
129 Diego, CA). P-values of  $<0.05$  were considered statistically significant.

130



## Results

### *Pre- and post-donation characteristics*

We included 105 female living kidney donors who were 41 [36-44] years old at donation, with a BMI of 25 [22-27] kg/m<sup>2</sup>. Before donation, the GFR was 118 (17) mL/min, rising to 128 (19) mL/min during dopamine. The ERPF was 405 (74) mL/min, rising to 496 (113) mL/min during dopamine. Pre-donation characteristics are shown in table 1 by a break-up of BMI at 25 kg/m<sup>2</sup>. A higher BMI was associated with elevated GFR, both when expressed nominally and after normalization to height, indicating overweight-associated “hyperfiltration” (figure 1A and 1B). The RFR was 10 (10) mL/min, with no difference between the BMI categories.

At 2 months after donation (57 [50-63] days; table 2), mean GFR was 76 (13) mL/min rising to 80 (12) during dopamine. The break-up by BMI shows that nominal and height-adjusted GFR were significantly higher in overweight donors (figure 1C and 1D). ERPF was 286 (49) mL/min, rising to 332 (65) mL/min during dopamine. Post-donation RFR was 4 (6) mL/min, with a remarkable difference between the BMI categories. In the donors with a BMI <25 kg/m<sup>2</sup> RFR was 6 (5) mL/min, whereas in donors with a BMI ≥ 25 kg/m<sup>2</sup> RFR was completely lost (1 (7) mL/min, p=0.002 vs. BMI <25 kg/m<sup>2</sup>). The absolute change in RFR from pre- to post-donation was significantly different between BMI groups (low BMI -4 (7) mL/min, vs. high BMI -8 (6) mL/min, p=0.01).

### *Association between BMI and renal hemodynamics*

BMI was positively associated with GFR, both before (st. β 0.31, p=0.001) and after donation (st. β 0.36, p<0.001). BMI was inversely associated with post-donation RFR (st. β -0.32, p=0.003), but not with pre-donation RFR (st. β 0.07, p=0.49). The association between BMI

154 and post-donation RFR was independent of donor GFR, age and blood pressure (st.  $\beta$  -0.33,  
155  $p=0.004$ , table 3). When excluding donors with a BMI over 35 ( $n=2$ ), the results of model  
156 remained materially similar (st.  $\beta$  -0.36,  $p=0.003$ ). There was no effect modification by age  
157 ( $p_{\text{interaction}}=0.62$ ). Furthermore, BMI was inversely associated with the absolute change in  
158 RFR before vs. after donation (st.  $\beta$  -0.24,  $p=0.02$ ).

159

## Discussion

In this study, we observed that BMI is inversely associated with RFR, measured by dopamine infusion, after kidney donation in women of childbearing age. Moreover, RFR was fully lost in overweight women after donation, suggesting that in the female kidney donor with a high BMI, RFR is consumed after kidney donation.

After kidney donation, vasodilatation occurs as a compensatory response to adapt to the single-kidney state(39). This results in a single-kidney GFR of approximately 66% of the prior two-kidney state, instead of approximately 50%(36). In this cohort of female donors of childbearing age we found a similar hemodynamic response (post-donation GFR was 64% of pre-donation GFR). Based on our results, we hypothesize that hyperfiltration due to the combination of overweight and donation prevents further increase in GFR in response to dopamine(3, 35).

Being overweight is associated with distinct renal hemodynamic effects, i.e. a rise in ERPF and a relatively greater rise in GFR. This results in a rise of filtration fraction (4), in particular when associated with a central fat distribution(20). These associations are also present in single kidneys, i.e. after donation (current data) and in transplanted kidneys(5). Only in the single kidney state is a negative association of BMI with the GFR response to dopamine observed. Recently it was shown that the higher GFR in overweight patients is associated with a higher single-nephron GFR. Additionally, this is associated with larger glomeruli, and with more glomerulosclerosis and arteriolosclerosis than expected for age(11). The latter supports the assumption that an elevated single nephron GFR contributes to glomerular injury(17). Unfortunately, data on single nephron GFR and RFR in single kidneys are lacking so far.

Prompted by the report on increased PE risk post-donation (15), we focused on women of childbearing age. Absence of pregnancy-induced renal vasodilation is a hallmark of PE(8, 12,25). Our data raise the hypothesis that loss of renal vasodilator capacity, as reflected by loss of RFR after donation in overweight women, could be involved in the increased risk for PE after donation. This hypothesis is also strengthened by the fact that obesity is an important risk factor for PE (42). Unfortunately, Garg et al do not report BMI and accordingly, it is unknown from their study, whether the donors with PE were overweight(15). Other possible factors in the increased risk of PE after donation include the loss of GFR, direct effects of obesity on placental development(34) or effects of high blood pressure(6). In our study, we found that the association between BMI and RFR was independent of blood pressure.

Our results are in line with previous studies showing that higher BMI is associated with more RFR loss post-donation in female and male donors(26, 32). Dopamine, a prominent vasodilator, was used to induce renal vasodilatation and hence estimate RFR. In line with prior studies RFR is thus assessed as the acute hemodynamic response to a pharmacological trigger(40). Dopamine is an endogenous catecholamine that acts on dopaminergic receptors, which are also present in the kidney(12). It thus elicits dilatation of arterioles, both afferent but predominantly efferent, resulting in a rise of renal blood flow and GFR(39). Because of safety concerns and cardiovascular effects of dopamine infusions, a low-dose is used for testing RFR. The renal hemodynamic response therefore does not reflect the maximum vasodilator capacity, which likely reduces the sensitivity of RFR to detect subtle changes in glomerular hemodynamics and microvasculature. Thus, we speculate that absence of an association between BMI and RFR before donation may be due to lack of sensitivity of RFR. Alternatively, differential effects of being overweight and dopamine on afferent-efferent vasomotor balance before and after donor nephrectomy may have been involved.

207 What could be the implications of a reduced RFR? The concept of RFR originates from the  
208 1980's, starting from the notion that nephron loss generally does not lead to a corresponding  
209 loss in GFR, as is readily apparent after kidney donation, indicating that the kidney has some  
210 form of functional reserve(27, 37). The hypothesis was that loss of reserve capacity might  
211 better indicate the extent of nephron loss than GFR and accordingly, that loss of RFR might  
212 be a useful prognostic parameter for future renal function(40). However, this hypothesis has  
213 not been substantiated, due to a general paucity of data on sufficiently powered cohorts where  
214 both RFR and long term follow-up are available. Cross-sectional studies found RFR to be  
215 inversely associated with old age(14) and advancing stages of CKD (2). The short-term  
216 prognostic effects of RFR after donation have been reported by our group (33), showing that  
217 pre-donation RFR has a modest predicting effect for GFR shortly- after donation(33). Work  
218 on long term follow-up is still in progress.

219 The main limitation of our paper is the lack of long-term renal data and lack of data on  
220 pregnancy outcomes of living kidney donors. Also, the predictive effect of BMI is subtle and  
221 we have insufficient data to adjust for use of contraceptives or menstrual cycle period, which  
222 both influence renal hemodynamics(7). However, the effect of BMI on RFR is consistent in  
223 donors with only mild overweight (we included only two donors with a BMI over 35). Our  
224 study does not have sufficient power to show effects of BMI on ERPF reserve capacity,  
225 which can be relevant since the exact mechanism of “hyperfiltration” after donation is not yet  
226 clarified and may be dependent on glomerular hypertrophy(21).

227 Strong points of our study include state-of-the-art renal hemodynamics measurements, with  
228 continuous <sup>125</sup>I-Iothalamate and <sup>131</sup>I-hippurate infusions, instead of per-bolus administration.  
229 Our study links a modifiable risk factor, namely overweight, to RFR in young kidney donors.

230 Further studies are needed to study the effect of weight interventions on RFR in overweight  
231 women of childbearing age.

232 In conclusion, this study shows that overweight women of childbearing age have a  
233 diminished RFR after kidney donation. Long-term studies should substantiate the role of  
234 reduced RFR on long-term renal outcome and PE. Since the incidence of overweight amongst  
235 donors is rising, and BMI is an independent risk factor for ESKD(16, 23), a clear  
236 understanding of the impact of lifestyle on living donation is warranted. Prospective studies  
237 should explore whether BMI reduction prior to conception is of benefit to overweight female  
238 kidney donors during and after pregnancy.

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240

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247    **Disclosures**

248    The authors of this manuscript have no conflicts of interest to declare.

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**Figure Captions:**

**Figure 1: GFR before and during dopamine in donors grouped according to BMI.**

(A) Pre-donation GFR. (B) Pre-donation GFR normalized for height. (C) Post-donation GFR  
(D) Post-donation GFR normalized for height. Donors with a BMI  $\geq 25$  kg/m<sup>2</sup> post-donation  
did not show a significant rise in GFR during dopamine (p=0.19).

401 **Table 1: Pre-donation donor characteristics**

Variable	All donors	BMI <25 (n=54)	BMI ≥25 (n=51)	P
Age (years)	41 [36-44]	41 [38-44]	41 [36-44]	0.37
Systolic blood pressure (mmHg)	120 (10)	118 (9)	121 (11)	0.09
Diastolic blood pressure (mmHg)	74 (8)	73 (8)	74 (8)	0.37
Use of antihypertensives, n (%)	2 (2%)	0 (0%)	2 (4%)	0.18
Weight (kilogram)	71 [63-82]	63 [59-68]	82 [77-85]	<0.001
GFR absolute (mL/min)	118 (17)	112 (13)	125 (18)	<0.001
GFR normalized for height* (mL/min/m)	70 (10)	66 (7)	73 (10)	<0.001
GFR per kidney <sup>†</sup> (mL/min)	59 (8)	56 (6)	63 (9)	<0.001
GFR during dopamine (mL/min)	128 (19)	122 (17)	135 (19)	0.001
GFR during dopamine per kidney <sup>†</sup> (mL/min)	64 (10)	61 (9)	68 (9)	0.001
GFR during dopamine normalized for height <sup>1</sup> (mL/min/m)	35 (5)	33 (4)	37 (5)	0.001
GFR during dopamine per kidney <sup>†</sup> per height* (mL/min/m)	38 (6)	36 (5)	40 (6)	0.001
Renal functional reserve (mL/min)	10 (10)	10 (11)	10 (10)	0.81
Renal functional reserve per kidney (mL/min)	5 (5)	5 (6)	5 (5)	0.81
ERPF (mL/min)	405 (74)	393 (70)	417 (78)	0.18
ERPF normalized for BSA (mL/min/1.73)	389 (76)	402 (79)	377 (71)	0.10
ERPF normalized for height (mL/min/m)	242 (45)	236 (45)	248 (45)	0.19
ERPF during dopamine (mL/min)	496 (113)	484 (107)	509 (118)	0.28
Filtration fraction (proportion)	0.30 (0.05)	0.29 (0.05)	0.30 (0.05)	0.14
Proteinuria (g/24h)	0.0 [0.0-0.2]	0.0 [0.0-0.2]	0.0 [0.0-0.2]	0.72
Albuminuria (mg/L)	1.3 [0.0-2.9]	1.0 [0.0-2.1]	1.5 [0.0-2.9]	0.61

402 GFR, Glomerular Filtration Rate (<sup>125</sup>I-Iothalamate); ERPF, Effective Renal Plasma Flow

403 (<sup>131</sup>I-hippurate)

404 \* calculated as GFR / height (meters)

405 <sup>†</sup> calculated as absolute GFR / 2

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408 **Table 2: Post-donation donor characteristics**

Variable	All donors	BMI <25 (n=54)	BMI ≥25 (n=51)	P
Systolic blood pressure (mmHg)	118 (11)	115 (11)	121 (11)	0.01
Diastolic blood pressure (mmHg)	73 (7)	73 (8)	74 (7)	0.30
Use of antihypertensives, n (%)	2 (2%)	0 (0%)	2 (4%)	0.18
Weight (kilogram)	70 [63-81]	63 [58-69]	81 [76-86]	<0.001
GFR absolute (mL/min)	76 (13)	70 (9)	82 (13)	<0.001
GFR normalized for height* (mL/min/m)	45 (7)	42 (5)	48 (8)	<0.001
GFR during dopamine (mL/min)	80 (12)	76 (10)	84 (13)	0.002
GFR during dopamine normalized for height* (mL/min/m)	47 (7)	45 (6)	49 (7)	0.005
Renal functional reserve (mL/min)	4 (6)	6 (5)	1 (7)	0.002
Renal functional reserve change† (mL/min)	-1 (7)	1 (7)	-4 (6)	0.003
ERPF (mL/min)	286 (49)	270 (45)	300 (49)	0.04
ERPF normalized for BSA (mL/min/1.73)	271 (47)	271 (48)	270 (47)	0.93
ERPF normalized for height (mL/min/m)	242 (45)	236 (45)	248 (45)	0.02
ERPF during dopamine (mL/min)	322 (65)	311 (63)	333 (67)	0.11
Filtration fraction (proportion)	0.28 (0.04)	0.27 (0.04)	0.29 (0.04)	0.14
Proteinuria (g/24h)	0.0 [0.0-0.2]	0.0 [0.0-0.1]	0.1 [0.0-0.2]	0.28
Albuminuria (mg/L)	2.3 [0.8-3.0]	2.3 [1.0-3.0]	2.3 [0.5-3.0]	0.57

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410 GFR, Glomerular Filtration Rate (<sup>125</sup>I-Iothalamate); ERPF, Effective Renal Plasma Flow  
 411 (<sup>131</sup>I-hippurate)

412 \* calculated as GFR / height (meters)

413 † calculated as post-donation RFR – pre-donation RFR per kidney

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**Table 3: Linear regression analysis of BMI and change in renal functional reserve**

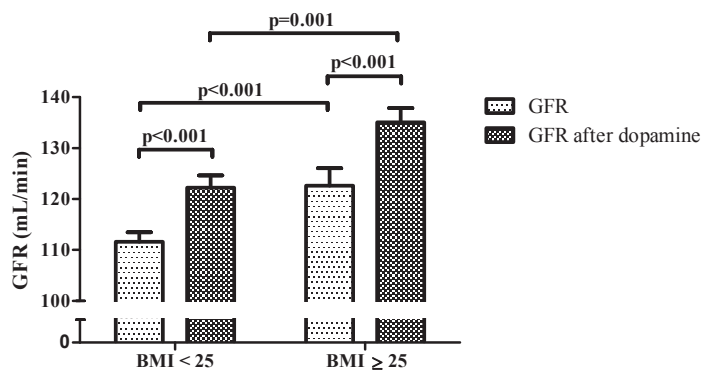
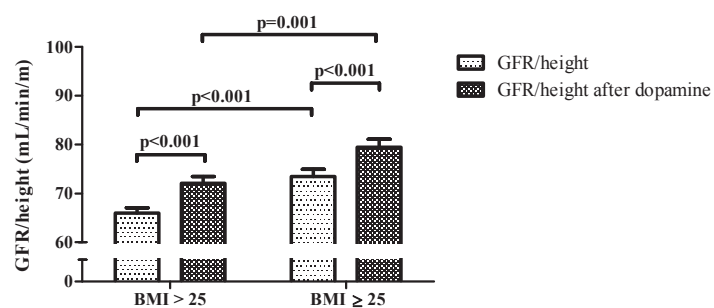
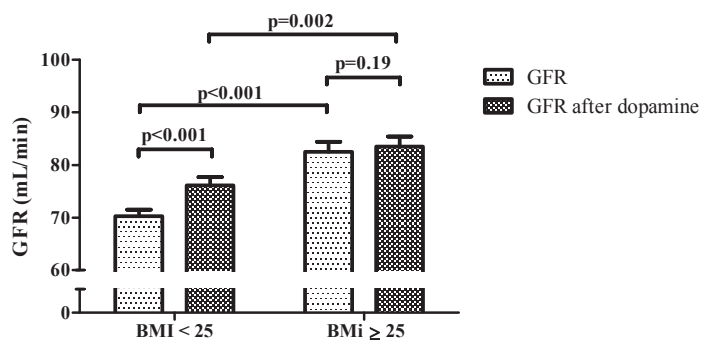
<b>Crude (<math>R^2=0.06</math>)</b>	<b>St. <math>\beta</math></b>	<b>P</b>
BMI	-0.33	0.003
<b>Model 2 (<math>R^2=0.21</math>)</b>		
Age	-0.29	0.008
Systolic blood pressure	0.20	0.12
Diastolic blood pressure	0.03	0.81
GFR	-0.09	0.42
BMI	-0.33	0.004

BMI, Body Mass Index ( $\text{kg}/\text{m}^2$ ); GFR, Glomerular Filtration Rate ( $^{125}\text{I}$ -Iothalamate)

Model 1: donor BMI at donation

Model 2: model 1 plus donor characteristics



**A****Predonation GFR per BMI category****B****Predonation GFR normalized for height per BMI category****C****Postdonation GFR per BMI category****D****Postdonation GFR normalized for height per BMI category**